IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Warren J. Scherer	Examiner:	Leslie A. Royds
Serial No.:	10/626,037	Group Art Unit:	1614
Confirmation No.:	1255	Docket:	512-160 RCE
Filed:	July 23, 2003	Dated:	June 11, 2009
For:	Methods of Treating Cutaneous Flushing Using Selective Alpha-2-Adrenergic Receptor Agonists		

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

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Michelle Flaherty
(Printed Name)

Signature: /michelle flaherty/

DECLARATION UNDER 37 C.F.R. §1.132

I, Guy F. WEBSTER, declare the following:

1. I am a board certified dermatologist, as evidenced in the attached curriculum vitae.

2. I have a B.A. in Biology-Molecular Biology and Genetics, a Ph.D. in Pathology, and a M.D. all from the University of Pennsylvania. I currently practice dermatology at Webster Dermatology PA in Hockessin, Delaware. I am also a Clinical Professor in the Department of Dermatology at Jefferson Medical College, where I was previously Vice Chair for Clinical Affairs in the Department of Dermatology. I am a Fellow of the American Dermatological Association.

3. I am familiar with the patent application identified above. I have reviewed the application, the pending office action dated March 11, 2009, and the four references cited by the examiner: Wymenga, et al., "Management of Hot Flushes in Breast Cancer Patients," *Acta Oncologica*, V. 41, No. 3, pp. 269-275 (2002); U.S. Patent Publication No. 2003/0229088 to Gil, et al.; Burke, et al. "Preclinical Evaluation of Brimonidine," *Survey of Ophthalmology*,

41(Supp.1), 1996, S9-S18; and Dictionary.com ("Topical" and "Transdermal," 2008). I am familiar with the response to the office action filed concurrently with this declaration. I am also familiar with the references cited by applicant in the response, *i.e.*, Dorland's Illustrated Medical Dictionary 2003 Ed. ("local" and "systemic" pages 1065 and 1848) and Shanler, et al. *Arch. Dermatol.* 143, 1369-1371 (2007).

4. Independent claims 1 and 36 are directed to a method of reducing cutaneous facial flushing caused by menopause-associated hot flashes by topically administering locally to the skin of a human the active ingredient so that the active ingredient acts locally to reduce cutaneous facial flushing.

5. To a person having ordinary skill in the art, local administration means that the active agent only affects the area to which it is applied. This is in contrast to transdermal administration, a form of systemic administration, whereby the active compound enters the bloodstream and is distributed throughout the body.

6. One cannot predict the effect of the local administration of a drug from the effect of systemic administration of the same drug. As an example, one would not reasonably expect to be able to reduce the discomfort of a headache by formulating aspirin in a cream, and rubbing the composition on one's forehead.

7. Wymenga appears to provide evidence that clonidine is not acting by agonizing alpha adrenergic receptors. For example, agonists of alpha-adrenoreceptors typically cause a reduction in blood pressure. However, in the same paragraph that discloses oral or transdermal clonidine to be effective in reducing flushes caused by normal menopause, Wymenga also discloses that in a study of the effect of oral clonidine on flushing in breast cancer patients, "[n]o effect on blood pressure was reported." See page 272, three lines from the end of the first partial paragraph.

8. According to the Shanler article mentioned above, there are at least six alpha adrenoreceptor subtypes. See page 1370, column 2, last sentence of the first full paragraph. It is difficult to predict how a certain alpha-adrenoreceptor subtype will affect a particular part of the

body. Each alpha-adrenoreceptor subtype is like an electrical switch. Each switch can be turned on or off by an agonist or antagonist. However, the effect of turning on or off one adrenoreceptor subtype may not be the same as the effect of a turning on or off a different receptor subtype. Moreover, the effect of an agonist or antagonist on an adrenoreceptor subtype in one part of the body may not be the same as the effect of an agonist or antagonist on the same adrenoreceptor subtype in a different part of the body.

9. It is clear that agonizing an alpha-adrenoreceptor may cause various unpredictable effects, such as vasodilation or vasoconstriction, that depend on the subtype of an adrenoreceptor as well as on its location in the body. The effects of an alpha-adrenoreceptor subtype can be very different from that of another alpha-adrenoreceptor subtype, indeed the opposite, depending on the subtype and location in the body.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. Further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application of any patent issued thereon.

Respectfully submitted,

Dated: 6/16/09

Guy F. Webster